that the inventors found that form I DHEA preparations can be contaminated with significant levels of form VI DHEA and that Chang's studies could not distinguish between DHEA preparations containing significant amounts (*i.e.*, greater than 15%) of form VI mixed with form I and substantially pure (*i.e.*, 85% or greater) form I preparations. Furthermore, because Chang *et al.* were not aware of the existence of form VI DHEA, the Chang article necessarily failed to enable the reproducible production of preparations containing at least 85% form I (*i.e.*, no more that 15% form VI) from form I:form VI mixtures, much less the production of preparations containing at least 90%, 95%, or 99% form I. Examiner Dees indicated that Applicants could expedite prosecution by addressing the purity of Chang's preparations.

Election/Restriction.

The Office Action states that all of the pending claims, except claim 9, are under examination, indicating that claim 9 has been withdrawn from consideration. As Applicants pointed out in the Amendment filed on May 7, 2002, the indication of claim 9 as withdrawn from consideration pursuant to a restriction requirement appears to be a typographical error. Specifically, the restriction requirement (dated October 4, 2002) divided claims 1-10 into Claim Group I (claims 1-4) and Claim Group II (claims 5-10). Applicants traversed the restriction requirement. In the first Office Action (dated February 12, 2002), the Examiner stated:

> On Applicant's [*sic*] request Examiner had reconsidered the restriction requirement and combined claims 1-4 of group I and claims 5-8 and 10 from group II for examination. Claims 1-4 are drawn to pharmaceutical formulations of DHEA and claims 5-8 and 9 are drawn to method [*sic*] for preparing formulations, [the] others are drawn to different formulations and methods for treatment of systemic lupus erythematosus, to prevention or reduction of loss of bone density, and treatment of chronic fatigue syndrome or fibromyalgia.

February 12 Office Action, page 2. Claims 9 and 10 both depend from claim 5, which relates to a method for preparing a solid DHEA formulation. Claim 9 relates to an embodiment in which the solid formulation is placed into a capsular container, and claim 10 relates to an embodiment in which the solid formulation is compressed to form a tablet. If the Examiner is seriously contending that claims 9 and 10 cannot be examined in the same application without undue burden, Applicants respectfully request the Examiner to clearly state this on the record. None of the Examiner's rationales for restriction set forth in the restriction requirement or in the February 12 Office Action

(and quoted above) provides any justification for restricting claim 9 away from the other claims under examination. Until the Examiner clearly indicates that she does not intend to examine claim 9 and provides a justification for this position, Applicants consider that the omission of claim 9 from the claims under examination was a typographical error. Accordingly, Applicants submit that all pending claims are under examination in the present application.

35 U.S.C. § 112, Second Paragraph.

Claims 1-8, 10, and 36-39 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite because the "term 'comprising cited in [the] claims is inclusive and fails to exclude unrecited steps." Office Action, page 2. The rejection is respectfully traversed.

When considering whether claims are definite under § 112, second paragraph, the "inquiry is merely to determine whether the claims do, in fact, set out and circumscribe a particular area with a reasonably degree of precision and particularity." *In re Moore*, 169 USPQ 236, 238 (C.C.P.A. 1971). If those skilled in the art can determine when they are practicing the claimed invention and when they are not, the metes and bounds of the claims are clear, and the claim cannot properly be rejected as indefinite.

Applicants first note that the Examiner's statement indicates that the Examiner clearly understood the meaning of the term "comprising." That is, the Examiner indicates that the claims, which use the transition "comprising" read on any composition including the specifically recited elements, regardless of the presence or absence of additional elements. Furthermore, the Examiner cites two cases that indicate that the meaning of the term "comprising" is clear and definite. In *Ex parte Davis*, 80 USPQ 448, 449 (Bd. App. 1948), the Board stated "the word 'comprising' alone . . . [is] synonymous with 'including.'" The Board concluded: "We regard the meaning of the terms 'comprising' and 'consisting of' to be well settled by numerous decisions . . . ." *Ex parte Davis*, 80 USPQ at 450. As the Examiner appears to recognize, *Ex part Gottzein*, 168 USPQ 176, 177 (Bd. App. 1969) clearly indicates that the term "comprising" "means . . . that the device covered by . . . [the] claims [at issue] may involve many more elements than those positively recited therein." Thus, the Office Action itself establishes that the term comprising is neither vague nor confusing in any way.

Moreover, the M.P.E.P. states:

> The transitional term "comprising", which is synonymous with "including," "containing," or "characterized by," is inclusive or open-

> ended and does not exclude additional, unrecited elements or method steps. Moleculon Research Corp. v. CBS, Inc., 793 F.2d 1261, 229 USPQ 805 (Fed. Cir. 1986); In re Baxter, 656 F.2d 679, 686, 210 USPQ 795, 803 (CCPA 1981); Ex parte Davis, 80 USPQ 448, 450 (Bd. App. 1948)("comprising" leaves "the claim open for the inclusion of unspecified ingredients even in major amounts").

M.P.E.P. § 2111.03.

In view of the well-settled meaning of the term "comprising," those skilled in the art would understand that claim 1, for example, which recites a "pharmaceutical formulation comprising dehydroepiandrosterone (DHEA), at least 85% of which is present as the form I polymorph, and at least one pharmaceutical excipient" reads on any composition having at least these two elements. Claim 5 recites a "method for preparing a solid DHEA formulation, said method comprising: mixing at least one solid pharmaceutical excipient with dehydroepiandrosterone (DHEA), at least 85% of which is present as the form I polymorph." One skilled in the art would thus understand that claim 5 reads on any method reciting this mixing step. Applicants submit that the only other independent claims, claims 36-39, are clear and definite for the same reasons as discussed above for claims 1 and 5.

As the metes and bounds of all of the pending claims would be readily understood by those of skill in the art, Applicants submit that claims 1-10 and 36-39 fully satisfy the definiteness requirement. Withdrawal of the rejection under § 112, second paragraph is therefore respectfully requested.

35 U.S.C. § 103(a).

Claims 1-8, 10, and 36-39 were rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Morales *et al.* (USPN 5,407,927) and Loria *et al.* (US 5,077,284) in combination with Chang *et al.* (J. Pharm. Sci. 84:1169-70 (1995)). Office Action, page 3. This rejection is respectfully traversed.

The Examiner relies on Morales and Loria as teaching "the formulation of DHEA for various methods of treatments and cites "especially lines 37-62, col. 1; lines 4-10 and lines 59-66, col. 12 in US 5,077,284 and lines 59-68, col. 2; lines 25-58, col. 3 and table 2 in col. 7 in US 5,407,927." Office Action, page 3.

To establish a *prima facie* case of obviousness, the Examiner must demonstrate that (1) all elements of the invention are found in the cited art; (2) the cited art provided motivation to

combine or, if necessary, modify these elements to arrive at the claimed invention; and (3) the cited art revealed that in making the claimed invention, those of ordinary skill in the art would have a reasonable expectation of success. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

All of the pending claims recite "dehydroepiandrosterone (DHEA), at least 85% of which is present as the form I polymorph." Applicants pointed out previously, and the Examiner does not dispute, that neither Morales nor Loria teach or suggest anything about the DHEA form(s) present in the preparations disclosed in these references. However, the Examiner notes:

> Chang et al. teaches solid state crystallization of DHEA and its polymorph (forms I-III). Furthermore, it discloses that form I is more stable than others.

Office Action, page 3.

Applicants respectfully point out that the claimed invention relates to compositions having ***at least 85%*** form I DHEA. So the proper focus of the obviousness inquiry is whether Chang teaches or suggests compositions having this high a concentration of form I. Moreover, the Examiner must also consider whether Chang teaches or suggests compositions having 90%, 95%, and 99% form I DHEA, as recited in dependent claims 2 and 6 (90%); 3, 7, 37, and 39 (95%); and 4 and 8 (99%).

The Examiner acknowledges that the claims relate to a specific polymorphic form of DHEA, but states:

> It would have been obvious to one skilled in the art at the time when the instant invention was made, to be motivated to prepare additional beneficial preparations and formulations of DHEA by using any polymorphic form of this compound especially form I and would expect the same results because when the compositions of the compound wold be prepared, it would be the same after dissolving in the solvent no matter what polymorphic form exists in the solid state.

Even assuming *arguendo* that one skilled in the art would be motivated to prepare additional preparations containing DHEA form I, Applicants submit that Chang does not teach or suggest DHEA preparations that are at least 85% form I, much less how to achieve such preparations.

In particular, Chang fails to present any convincing evidence that such a preparation was prepared. Chang discloses form I-containing preparations, but merely assumes that these preparations were pure (see Chang, page 1173, col. 2). As Applicants' specification points out, this assumption was incorrect. Chang was unaware of the likelihood that their form I preparation was

contaminated with a heretofore unknown form, namely form VI. In particular, note the passage at page 5, lines 7-20 of Applicants' specification, which explains that Chang's supposedly pure form I was actually a mixture of form I and form VI. To prepare truly pure form I, Applicants crystallized DHEA from 2-propanol, acetone, or acetonitrile, as described by Chang, and then carried out an additional step not performed by Chang. Specifically, this step entailed "suspending the precipitate from the first step in ethyl acetate (about 100 mL/30 g of DHEA) and stirring the resulting slurry at room temperature for about one week, followed by filtration." Applicants confirmed the purity of this preparation by ^{13}C-solid state NMR (^{13}C-SSNMR) analysis, a technique not employed by Chang.

Chang performed studies in which different preparations were mixed and then measured using X-ray powder diffraction. Chang, page 1173-1174. Chang concluded from these studies that: "These results indicate that the purities of forms I-III and S1 are as high as 95%, and X-ray powder diffraction can ***potentially*** be employed as a method of estimating the purity of polymorphs of DHEA." Chang, page 1175, col. 1 (emphasis added). Applicants point out that these results were obtained using an analytical method that was unable to distinguish form I from form VI. As Applicants have demonstrated, ^{13}C-SSNMR is the only analytical method known to be capable of this distinction. Because Chang did not use ^{13}C-SSNMR, Chang's conclusions regarding the purity of their form I preparation are not scientifically credible. One skilled in the art would therefore discount Chang's claim to have prepared a 95% form I DHEA preparation. Moreover, because Chang was unaware of the existence of contaminating form VI, Chang provides no guidance as to how to reliably produce form I DHEA free of substantial (*e.g.*, greater than 15%) form VI.

The Examiner states that "[d]ifferent polymorphic forms are not patentable over each other in the absence of unexpected properties." Office Action, page 3. Applicants do not concede this point, but need not rebut it as Applicants claims are directed to a preparation having a particular polymorphic form ***at a specific concentration***. Therefore, the patentability of polymorphs over one another is irrelevant. Instead, the question the Examiner must address is whether Chang would lead one skilled in the art to produce preparations containing at least 85%, 90%, 95%, or 99% form I DHEA. Applicants respectfully submit that Chang provides no credible basis for the contention that one skilled in the art, following Chang, could produce such preparations. To the contrary, Applicants found that form I DHEA preparations can be contaminated with significant levels of form VI DHEA and that Chang's studies could not distinguish between DHEA preparations containing

significant amounts (*i.e.*, greater than 15%) of form VI mixed with form I and substantially pure (*i.e.*, 85% or greater) form I preparations. Furthermore, because Chang *et al.* were not aware of the existence of form VI DHEA, the Chang article necessarily failed to enable the reproducible production of preparations containing at least 85% form I (*i.e.*, no more that 15% form VI) from form I:form VI mixtures, much less the production of preparations containing at least 90%, 95%, or 99% form I.

The only statement in the Office Action that addresses the purity element in the recited claims is that "[i]t had been held that . . . changing the form, purity or other characteristics of an old product does not render the novel form patentable where the difference in form, purity or characteristic was inherent in or rendered obvious by the prior art." Office Action, page 4 (citing *In re Cofer*, 354 F.2d 664; 148 USPA 268, 271 (CCPA 1966). The Examiner appears to believe that this rule of law dictates that a higher purity form of an old product is *per se* unpatentable. However, this interpretation overlooks the second half of the sentence, which sets forth the condition that "the difference in form, purity or characteristic was inherent in or rendered obvious by the prior art." Applicants submit that Chang manifestly fails to satisfy this condition and therefore that the Examiner's reliance on *Cofer* is misplaced.

In fact, a careful reading of *Cofer* indicates that this decision supports Applicants' position, rather than the Examiner's. The claims at issue in *Cofer* related to a compound termed 2,2-B in a novel form, namely as free-flowing crystals. As the court noted:

> According to appellant's specification no method has yet been described which permits production of pure 2,2-B directly by the reaction of epichlorohydrin with "Bisphenol A." Prior attempts to recover 2,2-B have resulted only in recovery of a relatively viscous liquid containing impurities which adversely affected the usefulness of epoxy resins prepared therefrom.

Cofer, 354 F.2d at 665. The Examiner had rejected the claims as obvious under 37 C.F.R. § 103 over references disclosing the viscous form of 2,2-B, and the Board of Patent Appeals and Interferences had affirmed this rejection. *Id.* at 665-66.

The court framed the issue in *Cofer* as follows:

> The basis for the rejection is, essentially, that the claimed product is merely a different form of a known compound, and, notwithstanding that some desirable results are obtained therefrom, since the product has the same utility as the art compound; the claimed product is deemed to be unpatentable thereover.

Id. at 666. The Examiner had argued that the difference in properties resulted only from a greater degree of purity and was therefore to be expected. *See id.* at 667. Applicants submit that the facts of *Cofer* are analogous to those of the present application. Specifically, in both cases, the claims were rejected as obvious over art disclosing as less pure form of the same material. In *Cofer*, the Board regarded the fact that the claimed product had the same utility as the prior-art product as dispositive of obviousness. In the present case, the Examiner takes the position that the form I DHEA in Applicants' composition has the same properties as the form I DHEA described by Chang and that this necessitates a finding of obviousness.

However, the *Cofer* court indicated that such considerations are not dispositive, stating:

> We think the board failed to address itself to other factors which must be given weight in determining whether the subject matter as a whole would have been obvious, namely, ***whether the prior art suggests the particular structure or form of the compound or composition as well as suitable methods of obtaining that structure or form***. The new form of the compound set forth in the claims is as much a part of the "subject matter as a whole" to be compared with the prior art as are other properties of the material which make it useful.

Cofer, 354 F.2d at 668 (emphasis added). Accordingly, the court reversed the rejection, concluding that "the record fails to support a holding that those skilled in the art should have known that 2,2-B would exist in crystalline form or that it would be known how to obtain such crystal." *Id.* The same rationale dictates that the § 103 rejection be withdrawn in the present case. That is, the record fails to support a conclusion that those skilled in the art would have known that DHEA preparations wherein at least 85% of the DHEA present was form I could be produced or how to produce them.

In a later case, *In re Irani*, 166 USPQ 24 (CC.PA 1970), the C.C.P.A. used the same rationale in reversing a § 103 rejection of a claim to a crystalline anhydrous ATMP. *Id.* at 25. The references cited in the § 103 rejection disclosed "glassy" (non-crystalline) ATMP. *Id.* The court explained the basis for the rejection as follows:

> The examiner was of the opinion that one skilled in the art knowing of Petrov's "glassy solid" form of ATMP would be motivated to attempt the preparation of crystalline anhydrous ATMP by the knowledge that some amino phosphonic acids exist in crystalline form (Kosolapoff and Bersworth) and that some amino phosphonic acids are useful as softeners, sequesterants, or chelating agents (Pikl and Bersworth).

Id. However, the court found that "even assuming that one skilled in the art could have predicted with reasonable certainty that crystalline anhydrous ATMP could be produced, we are not convinced the this record that it would also have been obvious *how* this could be achieved." *Id.*

The facts of *Irani* are analogous to the facts of the present case. First, one skilled in the art could not have predicted with reasonable certainty that high purity (85% or higher) form I DHEA preparations could be produced because none of the cited references provides a reliable means of even measuring the purity of form I DHEA preparations. Second, even if it were reasonable to suppose that such high-purity form I DHEA preparations could be produced, the record is devoid of any indication of how this may be achieved. Specifically, the record neither teaches nor suggests any means of removing contaminating form VI from form I DHEA preparations.

In view of the foregoing, Applicants submit that the authority cited by the Examiner, when properly applied to the facts of the present case, leads to the conclusion that the pending claims are patentable over the cited references. Of the cited references, Chang is the only one that discusses form I DHEA. However, Chang's purity estimates are not scientifically credible because of the likelihood that Chang's preparations were contaminated with a significant amount of form VI DHEA. Moreover, Chang provides no hint as to how to obtain high-purity form I preparations free of form VI. Therefore, Chang, taken alone or with the other cited references, fails to teach or suggest preparations having 85% form I DHEA. Chang provides no motivation to remove form VI DHEA from form I DHEA to yield high-purity form I preparations because Chang was unaware of the existence of form VI. Chang therefore necessarily fails to provide a reasonable expectation that such high-purity form I DHEA preparations could be achieved. Because none of the elements of a *prima facie* case have been met, Applicants respectfully request withdrawal of the § 103 rejection.

Conclusion

In view of the foregoing, Applicants believe that all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (510) 769-3509.

QUINE INTELLECTUAL PROPERTY LAW GROUP, P.C.
P.O. BOX 458
Alameda, CA 94501
Tel: 510 337-7871
Fax: 510 337-7877

Respectfully submitted,

Emily M. Haliday
Reg. No: 38,903